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Cost-effectiveness as a guide to pricing a new pharmaceutical product

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This paper applies cost-effectiveness analysis to a major clinical innovation. Using a structured survey of professional judgements to obtain estimates of research costs associated with its use, the analysis suggests that a premium price for the drug decided on by the manufacturer would be justified on the grounds that it could provide substantial cost savings. The results obtained appeared sensitive neither to variations in the cost assumptions, nor to alternative definitions of effectiveness. In general, *ex ante* economic evaluation of a new medicine before price setting is shown to be both feasible and informative.

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Earlier research examined pharmaceutical innovations in aggregate and showed how prices reflect market conditions such as innovation 'quality', potential entry and price elasticity.[1,2] Subsequently, individual product studies used techniques of cost-benefit analysis.[3,4] These studies were *ex post* in that the products had already been marketed at particular prices. More recently, in an *ex ante* study, Buxton and O'Brien[5] applied cost-effectiveness analysis to a still-to-be-launched new pharmaceutical product the price of which had yet to be set, but for which clinical data on effectiveness were available. This paper builds on that study using improved cost data. Buxton and O'Brien[5] used 'crude estimates' of costs. In this study representative costs were obtained empirically from structured sample surveys of clinical and administrative experts.

The paper examines how cost-effectiveness analysis can be used to guide pricing decisions. In particular it addresses the case of ondansetron, a newly available anti-emetic drug explicitly designed for use by patients undergoing chemo- or radiotherapy.

Clinical trial data[6] available prior to the pricing decision, comparing the anti-emetic properties of intravenous ondansetron with the previous drug of choice, metoclopramide, suggest that cancer patients receiving cisplatin chemotherapy plus ondansetron are less likely to suffer from both significant emesis and significant side-effects. How can clinical superiority justifiably be reflected in corporate pricing policy, given the background of a health care delivery system under constant pressure to contain costs? This is the issue that this paper addresses.

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Cost minimisation and cost-effectiveness

Optimal cost-containment may not necessarily imply cost minimisation. Cost-minimisation analysis compares two or more alternative courses of action, e.g. of medical treatment, and assumes they are either identical, or sufficiently similar for any differences to be ignored. Cost-effectiveness analysis, however, compares the costs to the level of outcome achieved by different methods. Thus if two anti-emetics can be used in chemotherapy but one is more effective, then it may be more cost-effective despite a higher purchase price.

Application of cost-effectiveness analysis to ondansetron

Data sources

The data used in this paper come from two sources. Clinical trial results were obtained from a British study.[6] A multi-centre double-blind crossover trial was carried out to compare the efficacy and safety of ondansetron with those of metoclopramide in the prophylaxis of acute nausea and vomiting induced by cisplatin-containing cancer chemo-therapy regimens. The researchers used a randomised crossover design with two treatment periods 3-4 weeks apart. Details of the alternative regimens applied over the 24-hour period are given in the questionnaire (available from the authors). The two subsamples, aged 29-69 years, were hospitalised and had a variety of primary tumour locations. The data used related primarily to three variables: (*i*) the presence or absence of significant emesis; (*ii*) the presence or absence of significant side-effects; and (*iii*) whether these side-effects were resolved. Definitions used in the trial for these terms are given in the questionnaire. The second set of data was economic not clinical. The clinical results can reasonably be presumed to be internationally transferable. Buxton and O'Brien's[5] cost estimates can be improved upon, however. Their study used 'crude estimates', not actual costs incurred. Furthermore, patterns of treatment and the mix of medical personnel employed vary between and also within countries, while the relative cost structures of hospitals are not homogeneous. This study collected actual local cost data and applied them to the clinical evidence. Two panels of South African clinical experts were established, one 'coastal' and one 'inland', drawn from different oncological centres throughout the country. The former met in Cape Town and the latter in Johannesburg. Each panel comprised an oncologist, an oncological nursing sister, a hospital pharmacist, a member of the South African Cancer Association and a senior hospital administrator. The cost data obtained thus spanned not only the regional divide but also the wide institutional differences between teaching hospitals, private clinics, large provincial hospitals and small town units.

Main analysis

Fig. 1 summarises the outcome of the clinical trial results in a schematic format common in the literature of clinical

decision analysis.[7,8] The outcome probabilities were derived directly from the original trial data.[6] The patients were divided into two mutually exclusive groups each of which had ten mutually exclusive possible outcomes or pathways (P1 to P10). For example, of the patients treated with ondansetron 75% suffered no significant emesis. Of this 75% a subset of 11% suffered significant side-effects, of which 17% were treated; 100% of those treated had the side-effects resolved.

The next step in the analysis was to compute the full usage costs of both ondansetron and metoclopramide. Full usage costs in the case of anti-emetics encompass the costs of dealing with the residual emesis and of coping with side-effects, other than emesis, of the treatment (whether caused by the anti-emetic or the chemotherapy). The direct price difference between metoclopramide therapy and ondansetron was obtained by using the manufacturers' selling price for the former and the price already set in the UK market for the latter, i.e. R48 for metoclopramide and R225 (£45) for ondansetron.

Fig. 1 also shows the total incremental costs of each pathway (i.e. exclusive of the prices of each product). These costs were obtained from the interview panels and represent the averages of the answers obtained. Table I provides the three cost-estimates used in the penultimate column of Fig. 1. Thus the pathway P2 has an incremental cost of R200 (the cost of dealing with emesis) + R217,87 (the cost of dealing with side-effects) + R20,62 (the cost of treating the side-effects) = R438,48.

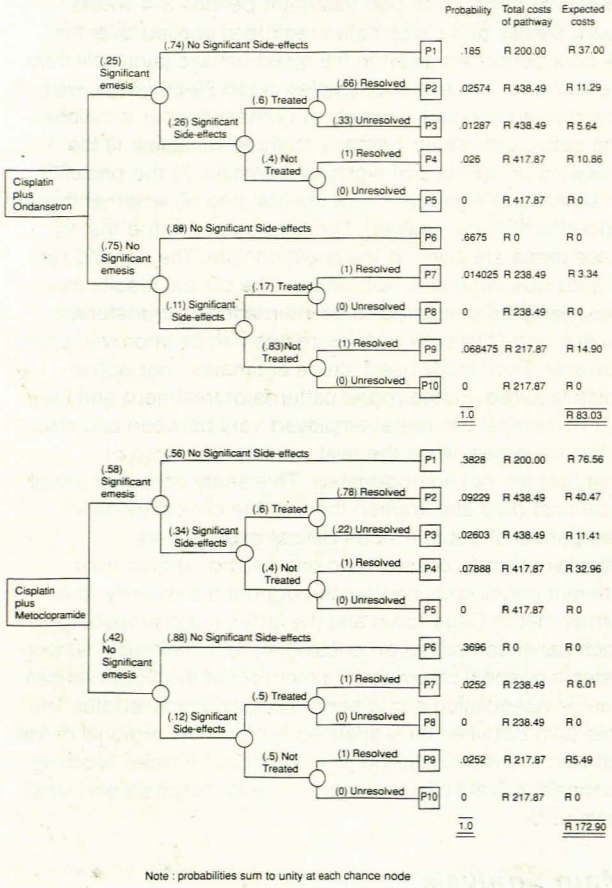

Fig. 1. Failure and side-effect costs for ondansetron and metoclopramide therapies.

Table I. Cost estimates

Additional cost of dealing with emesis (R)	
(per patient with significant emesis)	
24 minutes of nursing time	5,20
Linen, disposables, etc.	10,00
Probability cost of additional day's hospitalisation	184,80
Total	200,00
Additional cost of dealing with side-effects (R)	
(per patient with significant side-effects)	
10,5 minutes of nursing time	2,27
Probability cost of additional day's hospitalisation	215,60
Total	217,87
Additional cost of treating side-effects (R)	
(per patient who received treatment)	
37,5 minutes of junior doctor's time	10,62
Drug costs	5,00
Dispensing overheads	5,00
Total	20,62

The 'average' or 'expected' figures given above were computed from 'worst case', 'best case' and 'most likely case' answers to the questionnaire. The computation was as follows:

$$\text{Expected value} = \frac{\text{best case} + (4 \times \text{most likely case}) + \text{worst case}}{6}$$

where 'expected' value is the calculated mean of a beta distribution, given that 'best' and 'worst' are the extreme values and 'most likely' the modal value of that distribution.

From these cost-estimates, and the known probabilities of the events in the pathways, the final column of Fig. 1 was computed, the total of which gives the expected or average total incremental direct cost of treating any given patient with each product: namely R172,90 for metoclopramide and R83,03 for ondansetron. If we now add the respective prices for each product we have:

	Ondansetron	*Metoclopramide*
Price	R225,00	R 48,00
Incremental cost	R 83,03	R172,90
	R308,03	R220,90

At this point we have effectively undertaken a cost-minimisation exercise which indicates that metoclopramide is the product of choice. However, had ondansetron been priced at R137,87, nearly three times the metoclopramide level, then it would have been the least costly product (see Appendix).

Cost-effectiveness analysis takes account of therapeutic differences in success. If 'success' is defined as no significant emesis, the ondansetron offers a 0,75 chance of success as against metoclopramide's 0,42 probability (Fig. 1). If 'success' entails an absence of side-effects, the respective probabilities are given in pathways 6 of Fig. 1. Ondansetron's success rate is 0,67 (0,75 × 0,89) as against metoclopramide's 0,37 (0,42 × 0,88); i.e. if 100 patients were treated with ondansetron, 67 would be successfully treated as against 37/100 patients on a metoclopramide regimen. The expected total expenditures on the respective groups of 100 patients would be R30 803 with ondansetron and R22 090 with metoclopramide. If these measures of differential effectiveness are taken into account then the following applies:

Effective cost per 'successfully' treated patient:
('success' = no emesis)

Metoclopramide R220,90 ÷ 0,42 = R523,80
Ondansetron R308,03 ÷ 0,75 = R410,67
('success' = no emesis *and* no side-effects)
Metoclopramide R220,90 ÷ 0,37 = R597,03
Ondansetron R308,03 ÷ 0,67 = R459,75

Irrespective of which measure of success is used, ondansetron is substantially more cost-effective than metoclopramide when its price is related both to its differential effectiveness and to its differential net treatment costs.

Sensitivity analysis

What would be the effect if, instead of using data relating to average nursing costs, doctor costs and hospitalisation costs, etc., we used cost figures 25% higher or costs 25% lower than those uncovered in our survey? In short, are the analyses and the results sensitive to reasonable changes in the underlying data or not? Table II summarises the calculation done to answer this question. The effect of using the alternative definition of success is negligible. In each of the three cases (base case, incremental costs 25% higher and 25% lower than base) ondansetron at a price of R225/day is more cost-effective than metoclopramide at R48/day.

Table II. Cost-effectiveness calculations

	Base case	Cost assumptions* 25% above base	25% below base
Cost per success (R) (no emesis)			
Ondansetron	410,67	438,38	383,00
Metoclopramide	523,80	628,86	423,02
Ratio	0,78	0,70	0,91
Cost per success (R) (no emesis, no side-effects)			
Ondansetron	459,75	490,73	428,76
Metoclopramide	597,03	713,83	480,19
Ratio	0,77	0,69	0,89

*Average costs.

The methodology assumes that the resources not used by the more cost-effective product will either be 'saved' or put to use elsewhere. In most cases this will be so. In the private health care sector medical aid expenditures will be lower per successful case treated while in the state sector provincial authorities or teaching hospitals with fixed resources will be able to use them for other patients and/or other ailments. Only if resources are highly idiosyncratic and not transferable does this assumption not hold. These circumstances are rare and not within the bounds of this discussion. A clinical analysis and not merely a cost-sensitivity one could also have been carried out. In other words, what would have been the impact of differing pathway probabilities? We are not qualified to suggest what parameter variations would be realistic. Even so, it must be borne in mind that our results relate to one particular clinical trial only and that that clinical result will also be stochastic not deterministic.

Conclusion

Cost-effectiveness analysis has limitations. Firstly, only success is valued. It is given a weighting of 1 against a 0 weighting for failure. Ideally, the relative utility from the patients' viewpoint of each of the different endpoints should be assessed. Secondly, the panels of experts overwhelmingly agreed that patient morale and quality of life were the main advantages of success. These certainly result in cost savings, but the panels may have underestimated the benefits. It is clear that a premium price for ondansetron therapy over the cost of metoclopramide can be justified. On the basis of cost-minimisation analysis, net costs would be equalised with an ondansetron price of R137,87 on base case event cost assumptions for dealing with emesis, with side-effects and of treating side-effects. If differential effectiveness is allowed for in terms of cost per success (where success equals no significant emesis and no significant side-effects) a base case price of R317 would equalise *cost-effectiveness* (see Appendix). With a range of alternative event costs, at a price of R225 ondansetron is consistently more cost-effective.

Appendix

This paper took the UK price as its benchmark. If no benchmark price is available but a price is sought which equalises net costs on a cost-minimising or cost-effectiveness basis then the following formulae developed by Buxton and O'Brien should be adopted:

$$\text{let } c_o = c_m \ldots . (1)$$
$$\text{or } c_o/e_o = c_m/e_m \ldots . (2)$$

where c and e are cost and effectiveness and the subscripts denote ondansetron and metoclopramide.

$$\text{If } c_o = P_o + c1_o \ldots . (3)$$
$$\text{and } c_m = P_m + c1_m \ldots . (4)$$

where the prime signs indicate the expected costs of emesis management (from Fig. 1); and if P_m = R48 then by substitution and rearrangement P_o = R137,87, the price which equalises c_o and c_m.

To find P_o where equation (2) is satisfied take e_m and e_o from the probability values of pathways (6) in Fig. 1. Thus:

$$\frac{P_o + 83{,}03}{0{,}67} = \frac{48 + 172{,}9}{0{,}37}$$

P_o = R317 QED.

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